

=> s neurotroph?(l)pyrrolidin?
17085 NEUROTROPH?
60174 PYRROLIDIN?
L1 31 NEUROTROPH? (L) PYRROLIDIN?

=> s l1 and py<1998
18297841 PY<1998
L2 4 L1 AND PY<1998

=> d bib hit 1-4

L2 ANSWER 1 OF 4 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2002:332684 CAPLUS
DN 136:340999
TI Preparation of amino acid derivatives as rotamase enzyme activity
inhibitors
IN Steiner, Joseph P.; Hamilton, Gregory S.
PA USA
SO U.S. Pat. Appl. Publ., 40 pp., Cont.-in-part of U.S. Ser. No. 359,351.
CODEN: USXXCO
DT Patent
LA English
FAN.CNT 8

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 2002052410	A1	20020502	US 2001-805249	20010314
	US 5614547	A	19970325	US 1995-479436	19950607 <--
	US 2002013344	A1	20020131	US 1995-551026	19951031
	RU 2269514	C2	20060210	RU 2000-115383	19960605
	US 6509477	B1	20030121	US 1999-359351	19990721
PRAI	US 1995-479436	A1	19950607		
	US 1995-551026	A2	19951031		
	US 1996-693003	B1	19960806		
	US 1999-359351	A2	19990721		
	RU 1997-111860	A3	19960605		

OS	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 2002052410	A1	20020502	US 2001-805249	20010314
	US 5614547	A	19970325	US 1995-479436	19950607 <--
	US 2002013344	A1	20020131	US 1995-551026	19951031
	RU 2269514	C2	20060210	RU 2000-115383	19960605
	US 6509477	B1	20030121	US 1999-359351	19990721

AB The invention relates to methods of using **neurotrophic** compds. having an affinity for FKBP-type immunophilins to stimulate or promote neuronal growth or regeneration and to prevent neuronal degeneration. Amino acid derivs. R1C(:X)CON(J)CHKCO-Y(CH2)nCHZR2 [n = 0-3; Y is CH2, O, NH, or alkylimino; Z and R2 are independently Ar, or cycloalkyl, cycloalkenyl, or Ar-(un)substituted alkyl or alkenyl, or TCH:C(Q)CH2-, where Q = H, alkyl or alkenyl; T is Ar or substituted cycloalkyl; Ar is an (un)substituted mono or bicyclic heterocyclic aromatic ring; R1 is U, where U is H, (un)substituted alkyl, alkoxy, alkenyl, alkenyloxy, cycloalkyl or cycloalkenyl; X is O or CH-U, provided that if R1 is H, then X is CH-U or if X is O then R1 is U; J is H, alkyl or benzyl; K is alkyl, benzyl or cyclohexylethyl; or J and K may be taken together to form a 5-7 membered heterocyclic ring which may contain O, S, SO or SO2] or their pharmaceutically acceptable salts are claimed. Thus, 3-(3,4,5-trimethoxyphenyl)propyl (2S)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-pyrrolidinecarboxylate was prepared by esterification of the acid and showed Ki = 0.025 µM for inhibition of rotamase and ED50 = 80 nM for neurite outgrowth in chick dorsal root ganglion (DRG) cultures.

L2 ANSWER 2 OF 4 CAPLUS COPYRIGHT 2006 ACS on STN

AN 2002:276521 CAPLUS
DN 136:310178
TI Preparation of amino acid derivatives as rotamase enzyme activity inhibitors
IN Steiner, Joseph P.; Hamilton, Gregory S.
PA USA
SO U.S. Pat. Appl. Publ., 39 pp., Cont.-in-part of U.S. Ser. No. 551,026.
CODEN: USXXCO
DT Patent
LA English
FAN.CNT 8

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 2002042377	A1	20020411	US 2001-873298	20010605
	US 5614547	A	19970325	US 1995-479436	19950607 <--
	US 2002013344	A1	20020131	US 1995-551026	19951031
	RU 2269514	C2	20060210	RU 2000-115383	19960605
	US 6509477	B1	20030121	US 1999-359351	19990721
PRAI	US 1995-479436	A1	19950607		
	US 1995-551026	A2	19951031		
	US 1996-693003	B1	19960806		
	US 1999-359351	A2	19990721		
	RU 1997-111860	A3	19960605		

OS MARPAT 136:310178

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 2002042377	A1	20020411	US 2001-873298	20010605
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	US 2002013344	A1	20020131	US 1995-551026	19951031
	RU 2269514	C2	20060210	RU 2000-115383	19960605
	US 6509477	B1	20030121	US 1999-359351	19990721

AB The invention relates to methods of using **neurotrophic** compds. having an affinity for FKBP-type immunophilins to stimulate or promote neuronal growth or regeneration and to prevent neuronal degeneration. Amino acid derivs. R1C(:X)CON(J)CHKCO-Y-Z [Y is O, NH, or alkylimino; Z is H, CHL-Ar, alkyl, alkenyl, cycloalkyl, cycloalkenyl or Ar-substituted alkyl or alkenyl, or TCH:C(Q)CH(L)-, where L and Q are H, alkyl or alkenyl; T is Ar or substituted cyclohexyl; Ar is 1- or 2-naphthyl, 2- or 3-furyl, 2-thienyl, 2-, 3- or 4-pyridyl, (un)substituted phenyl; R1 is U, where U is H, (un)substituted alkyl, alkoxy, alkenyl, alkenyloxy, cycloalkyl or cycloalkenyl; X is O or CH-U, provided that if R1 is H, then X is CH-U or if X is O then R1 is U; J is H, alkyl or benzyl; K is alkyl, benzyl or cyclohexylethyl; or J and K may be taken together to form a 5-7 membered heterocyclic ring which may contain O, S, SO or SO2] or their pharmaceutically acceptable salts are claimed. Thus, 3-(3,4,5-trimethoxyphenyl)propyl (2S)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-pyrrolidinecarboxylate was prepared by esterification of the acid and showed Ki = 0.025 μ M for inhibition of rotamase and ED50 = 80 nM for neurite outgrowth in chick dorsal root ganglion (DRG) cultures.

L2 ANSWER 3 OF 4 CAPLUS COPYRIGHT 2006 ACS on STN

AN 1999:45148 CAPLUS

DN 130:110640

TI Preparation of proline derivatives as inhibitors of rotamase enzyme activity

IN Hamilton, Gregory S.; Steiner, Joseph P.

PA GPI NIL Holdings, Inc., USA

SO U.S., 27 pp., Cont.-in-part of U.S. 5,614,547.

CODEN: USXXAM

DT Patent

LA English

FAN.CNT 8

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
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PI	US 5859031	A	19990112	US 1996-650461	19960521
	US 5614547	A	19970325	US 1995-479436	19950607 <--
	CA 2206799	AA	19961219	CA 1996-2206799	19960605 <--
	CA 2206799	C	20051227		
	CA 2352900	AA	19961219	CA 1996-2352900	19960605 <--
	WO 9640633	A1	19961219	WO 1996-US9701	19960605 <--
	W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG				
	RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN				
	AU 9661062	A1	19961230	AU 1996-61062	19960605 <--
	AU 703118	B2	19990318		
	GB 2305176	A1	19970402	GB 1996-24257	19960605 <--
	GB 2305176	B2	19991222		
	EP 769006	A1	19970423	EP 1996-918384	19960605 <--
	EP 769006	B1	20001108		
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	DE 19680256	T	19970619	DE 1996-19680256	19960605 <--
	DE 19680256	C2	20030430		
	CH 688775	A	19980313	CH 1996-2790	19960605
	CN 1187188	A	19980708	CN 1996-194554	19960605
	GB 2324527	A1	19981028	GB 1998-15112	19960605
	GB 2324527	B2	19991222		
	GB 2325230	A1	19981118	GB 1998-17938	19960605
	BR 9608444	A	19990105	BR 1996-8444	19960605
	GB 2332673	A1	19990630	GB 1999-5606	19960605
	ES 2131457	A1	19990716	ES 1996-50030	19960605
	ES 2131457	B1	20000401		
	JP 2000503626	T2	20000328	JP 1997-501958	19960605
	JP 3561843	B2	20040902		
	EP 992492	A1	20000412	EP 1999-126231	19960605
	EP 992492	B1	20040825		
	R: BE, FR, GR, IT, NL, MC, IE				
	JP 2000169444	A2	20000620	JP 1999-235727	19960605
	JP 2000204048	A2	20000725	JP 1999-43437	19960605
	EE 200000317	A	20010615	EE 2000-200000317	19960605
	ES 2170628	A1	20020801	ES 1999-50069	19960605
	ES 2170628	B1	20030616		
	SG 94343	A1	20030218	SG 1999-6131	19960605
	SG 94722	A1	20030318	SG 1999-6130	19960605
	NZ 510086	A	20030328	NZ 1996-510086	19960605
	CZ 292529	B6	20031015	CZ 1997-2330	19960605
	SG 99293	A1	20031027	SG 1999-5533	19960605
	IL 134562	A1	20040620	IL 1996-134562	19960605
	EP 1433781	A1	20040630	EP 2004-7801	19960605
	R: BE, FR, GR, IT, NL, MC, IE				
	CN 1542001	A	20041103	CN 2004-10001996	19960605
	TR 200001644	T2	20041221	TR 2000-200001644	19960605
	CZ 295106	B6	20050518	CZ 2000-315	19960605
	RU 2269514	C2	20060210	RU 2000-115383	19960605
	TW 453992	B	20010911	TW 1996-85113067	19961024
	ZA 9608984	A	19980625	ZA 1996-8984	19961025
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	SE 523522	C2	20040427		
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	NO 317447	B1	20041101		
	BG 103977	A	20001130	BG 1999-103977	19971127
	LV 11991	B	19980720	LV 1997-243	19971203

LT 4484	B	19990325	LT 1998-1	19980106
HK 1013287	A1	20000616	HK 1998-114580	19981222
HK 1022307	A1	20010803	HK 2000-100914	19981222
AU 9935062	A1	19990819	AU 1999-35062	19990615
AU 742575	B2	20020110		
AU 9935063	A1	19990819	AU 1999-35063	19990615
AU 733685	B2	20010524		
SE 9903136	A	19990906	SE 1999-3136	19990906
SE 527193	C2	20060117		
DK 9901518	A	19991022	DK 1999-1518	19991022
DK 9901519	A	19991022	DK 1999-1519	19991022
US 6500959	B1	20021231	US 2000-605475	20000628
GR 3035326	T3	20010430	GR 2001-400154	20010131
US 2004049046	A1	20040311	US 2002-219887	20020816
PT 102940	A	20030930	PT 2003-102940	20030414
SE 2004000359	A	20040217	SE 2004-359	20040217
US 2005272780	A1	20051208	US 2005-166220	20050627
PRAI US 1995-479436	A2	19950607		
US 1996-650461	A	19960521		
AU 1996-61062	A3	19960605		
CA 1996-2206799	A3	19960605		
EP 1996-918384	A3	19960605		
EP 1999-126231	A3	19960605		
GB 1996-24257	A3	19960605		
IL 1996-121621	A3	19960605		
JP 1997-501958	A3	19960605		
RU 1997-111860	A3	19960605		
WO 1996-US9701	W	19960605		
US 1997-833629	A1	19970408		
US 2000-605475	A1	20000628		
US 2002-219887	B3	20020816		
OS MARPAT 130:110640				

RE.CNT 76 THERE ARE 76 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
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PI	US 5859031	A	19990112	US 1996-650461	19960521
	US 5614547	A	19970325	US 1995-479436	19950607 <--
	CA 2206799	AA	19961219	CA 1996-2206799	19960605 <--
	CA 2206799	C	20051227		
	CA 2352900	AA	19961219	CA 1996-2352900	19960605 <--
	WO 9640633	A1	19961219	WO 1996-US9701	19960605 <--
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	AU 9661062	A1	19961230	AU 1996-61062	19960605 <--
	AU 703118	B2	19990318		
	GB 2305176	A1	19970402	GB 1996-24257	19960605 <--
	GB 2305176	B2	19991222		
	EP 769006	A1	19970423	EP 1996-918384	19960605 <--
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	DE 19680256	T	19970619	DE 1996-19680256	19960605 <--
	DE 19680256	C2	20030430		
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JP 3561843	B2	20040902		
EP 992492	A1	20000412	EP 1999-126231	19960605
EP 992492	B1	20040825		
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JP 2000204048	A2	20000725	JP 1999-43437	19960605
EE 200000317	A	20010615	EE 2000-200000317	19960605
ES 2170628	A1	20020801	ES 1999-50069	19960605
ES 2170628	B1	20030616		
SG 94343	A1	20030218	SG 1999-6131	19960605
SG 94722	A1	20030318	SG 1999-6130	19960605
NZ 510086	A	20030328	NZ 1996-510086	19960605
CZ 292529	B6	20031015	CZ 1997-2330	19960605
SG 99293	A1	20031027	SG 1999-5533	19960605
IL 134562	A1	20040620	IL 1996-134562	19960605
EP 1433781	A1	20040630	EP 2004-7801	19960605
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CN 1542001	A	20041103	CN 2004-10001996	19960605
TR 200001644	T2	20041221	TR 2000-200001644	19960605
CZ 295106	B6	20050518	CZ 2000-315	19960605
RU 2269514	C2	20060210	RU 2000-115383	19960605
TW 453992	B	20010911	TW 1996-85113067	19961024
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ZA 9608983	A	19980727	ZA 1996-8983	19961025
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SE 9604098	A	19961208	SE 1996-4098	19961108 <--
SE 523522	C2	20040427		
US 5795908	A	19980818	US 1997-787161	19970123
US 6140357	A	20001031	US 1997-833629	19970408
NO 9704213	A	19971204	NO 1997-4213	19970912 <--
NO 317447	B1	20041101		
BG 103977	A	20001130	BG 1999-103977	19971127
LV 11991	B	19980720	LV 1997-243	19971203
LT 4484	B	19990325	LT 1998-1	19980106
HK 1013287	A1	20000616	HK 1998-114580	19981222
HK 1022307	A1	20010803	HK 2000-100914	19981222
AU 9935062	A1	19990819	AU 1999-35062	19990615
AU 742575	B2	20020110		
AU 9935063	A1	19990819	AU 1999-35063	19990615
AU 733685	B2	20010524		
SE 9903136	A	19990906	SE 1999-3136	19990906
SE 527193	C2	20060117		
DK 9901518	A	19991022	DK 1999-1518	19991022
DK 9901519	A	19991022	DK 1999-1519	19991022
US 6500959	B1	20021231	US 2000-605475	20000628
GR 3035326	T3	20010430	GR 2001-400154	20010131
US 2004049046	A1	20040311	US 2002-219887	20020816
PT 102940	A	20030930	PT 2003-102940	20030414
SE 2004000359	A	20040217	SE 2004-359	20040217
US 2005272780	A1	20051208	US 2005-166220	20050627

AB **Neurotrophic** N-glyoxyl prolyl esters R1COC(:X)-L-Pro-O-Z [R1 = alkyl or alkenyl optionally substituted by cycloalkyl or aryl groups; X = O, S; Z = (un)substituted alkyl or alkenyl], which have an affinity for FKBP-type immunophilins, were prepared for use as inhibitors of the enzyme activity associated with immunophilin proteins, in particular peptidyl-prolyl isomerase (rotamase) enzyme activity. Thus, 3-phenylpropyl (2S)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-pyrrolidinecarboxylate was prepared and showed apparent Ki value 42 for inhibition of rotamase activity.

AN 1998:599365 CAPLUS
 DN 129:198015
 TI Rotamase enzyme activity inhibitors
 IN Steiner, Joseph P.; Hamilton, Gregory S.
 PA GPI Nil Holdings, Inc., USA
 SO U.S., 16 pp., Cont.-in-part of U. S. Ser. No. 551,026, abandoned.
 CODEN: USXXAM
 DT Patent
 LA English
 FAN.CNT 8

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 5801197	A	19980901	US 1996-645149	19960513
	US 2002013344	A1	20020131	US 1995-551026	19951031
	CA 2236328	AA	19970509	CA 1996-2236328	19960826 <--
	WO 9716190	A1	19970509	WO 1996-US13624	19960826 <--
	W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN				
	RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN				
	AU 9668573	A1	19970522	AU 1996-68573	19960826 <--
	AU 713302	B2	19991125		
	EP 859614	A1	19980826	EP 1996-929014	19960826
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	CN 1205635	A	19990120	CN 1996-199127	19960826
	JP 11514643	T2	19991214	JP 1996-517308	19960826
	NO 9801903	A	19980630	NO 1998-1903	19980427
	LV 12102	B	19981020	LV 1998-85	19980625
PRAI	US 1995-551026	B2	19951031		
	US 1996-645149	A	19960513		
	WO 1996-US13624	W	19960826		

OS MARPAT 129:198015

RE.CNT 173 THERE ARE 173 CITED REFERENCES AVAILABLE FOR THIS RECORD

ALL CITATIONS AVAILABLE IN THE RE FORMAT

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 5801197	A	19980901	US 1996-645149	19960513
	US 2002013344	A1	20020131	US 1995-551026	19951031
	CA 2236328	AA	19970509	CA 1996-2236328	19960826 <--
	WO 9716190	A1	19970509	WO 1996-US13624	19960826 <--
	W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN				
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	AU 9668573	A1	19970522	AU 1996-68573	19960826 <--
	AU 713302	B2	19991125		
	EP 859614	A1	19980826	EP 1996-929014	19960826
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, FI				
	CN 1205635	A	19990120	CN 1996-199127	19960826
	JP 11514643	T2	19991214	JP 1996-517308	19960826
	NO 9801903	A	19980630	NO 1998-1903	19980427
	LV 12102	B	19981020	LV 1998-85	19980625

ST rotamase enzyme inhibitor pyrrolidinecarboxylate;
 neurotrophic pipecolic acid deriv

=> s (carboxylic(1)carboxylate(1)prodrug?)

235433 CARBOXYLIC

67489 CARBOXYLATE

14733 PRODRUG?

L5 22 (CARBOXYLIC(L)CARBOXYLATE(L)PRODRUG?)

=> s l5 and py<1998

18297841 PY<1998

L6 7 L5 AND PY<1998

=> d bib hit 1-7

L6 ANSWER 1 OF 7 CAPLUS COPYRIGHT 2006 ACS on STN

AN 1997:805509 CAPLUS

DN 128:136107

TI Acyloxymethyl as a drug protecting group: part 4. The hydrolysis of tertiary amidomethyl ester prodrugs of carboxylic acid agents

AU Iley, Jim; Moreira, Rui; Calheiros, Teresa; Mendes, Eduarda

CS Chemistry Department, The Open University, Milton Keynes, MK7 6AA, UK

SO Pharmaceutical Research (1997), 14(11), 1634-1639

CODEN: PHREEB; ISSN: 0724-8741

PB Plenum Publishing Corp.

DT Journal

LA English

RE.CNT 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD

ALL CITATIONS AVAILABLE IN THE RE FORMAT

SO Pharmaceutical Research (1997), 14(11), 1634-1639

CODEN: PHREEB; ISSN: 0724-8741

AB Novel tertiary amidomethyl esters were synthesized and evaluated as potential **prodrugs** of **carboxylic** acid agents.

Hydrolysis of the title compds. in buffer solns. and in plasma were studied by UV spectroscopy and HPLC. Amidomethyl esters were hydrolyzed by acid-catalyzed, base-catalyzed and pH-independent pathways. Both the acid-catalyzed, kH^+ , and pH-independent processes, k_0 , were strongly affected by the electronic and steric nature of the N-substituent in the pro-moiety. For both processes, the electronic effect exerted greater influence, and electron-withdrawing substituents retarded reaction. The pH-independent hydrolysis of amidomethyl esters were dependent on the pK_a of the **carboxylate** leaving group, giving a Bronsted β_{lg} value of -0.91. The base-catalyzed, KOH^- , pathway was mainly affected by the steric bulk of the nitrogen substituents in the amide moiety, the reactivity being reduced with larger N-substituents. Hydrolysis in human plasma appeared to be mediated by enzymic processes and is dependent upon the steric bulk in the **carboxylic** acid moiety. Plasma hydrolysis rates were inversely dependent on the lipophilicity of the ester. Derivs. containing the Et hippurate carrier are useful **prodrugs** for **carboxylic** acid-containing drugs with $pK_a > 3,5$, such as non-steroidal anti-inflammatory agents and valproic acid.

L6 ANSWER 2 OF 7 CAPLUS COPYRIGHT 2006 ACS on STN

AN 1997:140702 CAPLUS

DN 126:126494

TI Ortho-Substituted Benzofused Macrocyclic Lactams as Zinc Metalloprotease Inhibitors

AU Ksander, Gary M.; de Jesus, Reynalda; Yuan, Andrew; Ghai, R. D.; Trapani, A.; McMartin, Colin; Bohacek, Regine

CS Res. Dep., Novartis Pharm. Corp., Summit, NJ, 07901, USA

SO Journal of Medicinal Chemistry (1997), 40(4), 495-505

CODEN: JMCMAR; ISSN: 0022-2623

PB American Chemical Society

DT Journal

LA English

RE.CNT 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD

ALL CITATIONS AVAILABLE IN THE RE FORMAT

SO Journal of Medicinal Chemistry (1997), 40(4), 495-505
CODEN: JMCMAR; ISSN: 0022-2623

AB The design and preparation of ortho-substituted benzofused macrocyclic lactams are described. The benzofused macrocyclic lactams were designed as neutral endopeptidase 24.11 (NEP) inhibitors. Docking studies were carried out in a model of thermolysin (TLN) using the MACROMODEL and QXP modeling programs to select suitable ring sizes. These studies predicted that the 11-, 12-, and 13-membered ring macrocyclic lactams would be active in both enzymes TLN and NEP. Good predictability of exptl. results, within this series, of binding to thermolysin and to a lesser extent to NEP was observed. A visual comparison, docked at the active site of TLN, is presented for thiorphan, a 10-membered ring macrocycle and an 11-membered ring benzofused macrocyclic lactam. Potent inhibition of both NEP and thermolysin was obtained. The 11-membered ring macrocycle, 2,3,4,5,6,7,8,9-octahydro-2(S)-mercapto-3-oxo-1H-4-benzazacycloundecine-5(S)-**carboxylic acid**, is the most potent inhibitor from this series of compds. (TLN IC50 = 68 nM; NEP IC50 = 0.9 nM). The effects of **prodrug** benzyl 2(R)-[(acetylthio)methyl]-2,3,4,5,6,7,8,9,10,11-decahydro-2-ox-1H-4-benzazacyclotridecine-5(S)-**carboxylate** administered at 10 mg/kg po on plasma atrial natriuretic peptide (ANP) levels in conscious rats was greater than 200% over a 4 h period.

L6 ANSWER 3 OF 7 CAPLUS COPYRIGHT 2006 ACS on STN

AN 1997:21631 CAPLUS

DN 126:69906

TI Angiotensin II-inhibitory action of candesartan cilexetil and its active metabolite, CV-11974, in rabbit aortic strips and conscious rats

AU Shibouta, Yumiko; Inada, Yoshiyuki; Ojima, Mami; Wada, Takeo; Noda, Masakuni; Sanada, Tsukasa; Kubo, Keiji; Kohara, Yasuhisa; Naka, Takehiko; Nishikawa, Kohei

CS Pharmaceutical Res. Div., Takeda Chem. Ind., Ltd., Japan

SO Yakuri to Chiryo (1996), 24(10), 2207-2213

CODEN: YACHDS; ISSN: 0386-3603

PB Raifu Saiensu Shuppan K.K.

DT Journal

LA Japanese

SO Yakuri to Chiryo (1996), 24(10), 2207-2213

CODEN: YACHDS; ISSN: 0386-3603

AB The angiotensin II (AII) antagonistic action of 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-1H-benzimidazole-7-**carboxylic acid** (CV-11974) was examined in an in vitro AII-induced contraction assay using rabbit aortic strips, and that of CV-11974 and its **prodrug**, (\pm)-1-(cyclohexyloxycarbonyloxy)ethyl 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-1H-benzimidazole-7-**carboxylate** (candesartan cilexetil:TCV-116), was examined in an in vivo assay system of AII-induced pressor response in conscious rats. CV-11974 selectively inhibited the AII-induced contraction of rabbit aortic strips in a noncompetitive manner (pD'2:10.08), but at 10 μ M it has no effects on the contraction induced by norepinephrine, KCl, serotonin, prostaglandin F2 α , or endothelin. EXP3174, a main metabolite of losartan, showed a mixed type of competitive and noncompetitive inhibition with a pD'2 value of 9.06 and a pA2 value of 10.20 for the AII-induced contraction. CV-11974 given i.v. and TCV-116 given orally inhibited the AII-induced pressor response in rats with ID50 values of 0.03 mg/kg and 0.07 mg/kg, resp. These effects of CV-11974 and TCV-116 were approx. 10 times and 40 times more potent than those of EXP3174 and losartan, resp. These results indicate that CV-11947 is a highly potent and selective AII antagonist and TCV-116 has a long-acting AII-inhibitory action in the rat.

L6 ANSWER 4 OF 7 CAPLUS COPYRIGHT 2006 ACS on STN

AN 1996:515414 CAPLUS

DN 125:276411

TI Synthesis and antiviral activity of N-4'-dihydropyridinyl and

dihydroquinolinylcarbonyl-2-hydroxymethyl-5-[cytosin-1'-yl]-1,3-oxathiolane derivatives against human immunodeficiency virus and duck hepatitis B virus

- AU Camplo, M.; Charvey-Faury, A. S.; Borel, C.; Turin, F.; Hantz, O.; Traubaud, C.; Niddam, V.; Mourier, N.; Graciet, J. C.; et al.
- CS Laboratoire de Chimie Biomoléculaire, Faculté des Sciences de Luminy, Marseille, 13288, Fr.
- SO European Journal of Medicinal Chemistry (1996), 31(7-8), 539-546
CODEN: EJMCA5; ISSN: 0223-5234
- PB Elsevier
- DT Journal
- LA English
- SO European Journal of Medicinal Chemistry (1996), 31(7-8), 539-546
CODEN: EJMCA5; ISSN: 0223-5234
- AB Dihydropyridine and dihydroquinoline derivs. of 2-hydroxymethyl-5-[cytosin-1'-yl]-1,3-oxathiolane ((±)-3TC) have been prepared. The N-4-nicotinate or the N-4-quinoline-**carboxylate** amides were obtained by reacting nicotinic or quinoline-**carboxylic** acids with (±)-3TC in the presence of DCC and HOBT. These derivs. were converted into their corresponding N-methylpyridinium and N-Me quinolinium salts by treatment with MeI in acetone. Reduction of the latter with Na₂S₂O₄ gave dihydropyridine and dihydroquinoline compds. The N-4-trifluorotoluidinonicotinate derivative was obtained from the coupling of niflumic acid and (±)-3TC using BOP and DIEA. The anti-HIV-1-activities of seven derivs. were determined in MT-4 infected cell cultures. Of these compds., the IC₅₀ values ranged from 0.1-100 μM, while the IC₅₀ for (±)-3TC was 0.1 μM. The anti-HBV activities were determined in infected duck hepatocytes. Anti-HBV activities of the (±)-3TC derivs. were half that of the parent drug (±)-3TC. The lipophilicity (partition coeffs.) of these compds. were determined. The dihydroquinoline **prodrugs** had greater lipophilicity than the dihydropyridine analogs.
- L6 ANSWER 5 OF 7 CAPLUS COPYRIGHT 2006 ACS on STN
- AN 1995:521057 CAPLUS
- DN 122:281858
- TI Effects of TCV-116 and CV-11974 on angiotensin II-induced responses in vascular smooth muscle cells
- AU Flesch, Markus; Ko, Yon; Seul, Claudia; Duesing, Rainer; Feltkamp, Heinrich; Vetter, Hans; Sachinidis, Agapios
- CS Medizinische Universitaets-Poliklinik, Wilhelmstr. 35-37, Bonn, 53111, Germany
- SO European Journal of Pharmacology, Molecular Pharmacology Section (1995), 289(2), 399-402
CODEN: EJPPET; ISSN: 0922-4106
- PB Elsevier
- DT Journal
- LA English
- SO European Journal of Pharmacology, Molecular Pharmacology Section (1995), 289(2), 399-402
CODEN: EJPPET; ISSN: 0922-4106
- AB (±)-1-(Cyclohexyloxycarbonyloxy)ethyl 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-1H-benzimidazole-7-**carboxylate** (TCV-116, Candesartan) and its active metabolite 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-1H-benzimidazole-7-**carboxylic** acid (CV-11974) are specific nonpeptide angiotensin AT₁ receptor antagonists. In the present study, the inhibitory potency of these two antagonists on the angiotensin II-induced responses in aortic vascular smooth muscle cells from Wistar Kyoto rats was investigated. The specific binding of ¹²⁵I-angiotensin II to cells was inhibited by CV-11974 and TCV-116 with a half-maximal inhibitory concentration (IC₅₀) of 3+10⁻¹¹ M and 1+10⁻⁹ M, resp. CV-11974 and TCV-116 inhibited the angiotensin II-induced increase in [3H]thymidine incorporation with an IC₅₀ of 3+10⁻¹⁰ and 5+10⁻⁹ M, resp. Both CV-11974 and TCV-116 (10⁻⁷

M) completely blocked the angiotensin II-induced increase in c-fos mRNA. The inhibitory potency of the metabolite CV-11974 was about 30-100-fold higher than that of the prodrug TCV-116.

L6 ANSWER 6 OF 7 CAPLUS COPYRIGHT 2006 ACS on STN

AN 1993:580705 CAPLUS

DN 119:180705

TI Nonpeptide angiotensin II receptor antagonists. Synthesis and biological activity of potential prodrugs of benzimidazole-7-carboxylic acids

AU Kubo, Keiji; Kohara, Yasuhisa; Yoshimura, Yoshinobu; Inada, Yoshiyuki; Shibouta, Yumiko; Furukawa, Yoshiyasu; Kato, Takeshi; Nishikawa, Kohei; Naka, Takehiko

CS Pharm. Res. Div., Takeda Chem. Ind., Ltd., Osaka, 532, Japan

SO Journal of Medicinal Chemistry (1993), 36(16), 2343-9

CODEN: JMCMAR; ISSN: 0022-2623

DT Journal

LA English

SO Journal of Medicinal Chemistry (1993), 36(16), 2343-9

CODEN: JMCMAR; ISSN: 0022-2623

AB In order to improve the oral bioavailability (BA) of 2-butyl-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-1H-benzimidazole-7-carboxylic acid (CV-11194; I; R = Bu) and 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-1H-benzimidazole-7-carboxylic acid (CV-11974; I; R = OEt), novel angiotensin II (AII) receptor antagonists, chemical modification to yield prodrugs has been examined. After selective tritylation of the tetrazole rings in I, treatment of N-tritylated benzimidazole-7-carboxylic acids II with a variety of alkyl halides, followed by deprotection with hydrochloric acid, afforded esters of I. Mainly 1-(acyloxy)alkyl esters and 1-[(alkoxycarbonyl)oxy]alkyl esters, double ester derivs., were synthesized. Their inhibitory effect on AII-induced pressor response in rats and oral BA were investigated. (Pivaloyloxy)methyl and (+)-1-[[[(cyclohexyloxy)carbonyl]oxy]ethyl esters of I showed marked increases in oral bioavailability which significantly potentiated the inhibitory effect of the parent compds. on AII-induced pressor response. Among them, (+)-1-[[[(cyclohexyloxy)carbonyl]oxy]ethyl 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-1H-benzimidazole-7-carboxylate (III, TCV-116) was selected as a candidate for clin. evaluation.

L6 ANSWER 7 OF 7 CAPLUS COPYRIGHT 2006 ACS on STN

AN 1993:573923 CAPLUS

DN 119:173923

TI Pharmacological profile of a highly potent and long-acting angiotensin II receptor antagonist, 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-1H-benzimidazole-7-carboxylic acid (CV-11974), and

its prodrug, (+)-1-(cyclohexyloxy)carbonyloxyethyl

2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-1H-benzimidazole-7-carboxylate (TCV-116)

AU Shibouta, Yumiko; Inada, Yoshiyuki; Ojima, Mami; Wada, Takeo; Noda, Masakuni; Sanada, Tsukasa; Kubo, Keiji; Kohara, Yasuhisa; Naka, Takehiko; Nishikawa, Kohei

CS Pharm. Res. Div., Takeda Chem. Ind., Osaka, Japan

SO Journal of Pharmacology and Experimental Therapeutics (1993), 266(1), 114-20

CODEN: JPETAB; ISSN: 0022-3565

DT Journal

LA English

TI Pharmacological profile of a highly potent and long-acting angiotensin II receptor antagonist, 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-1H-benzimidazole-7-carboxylic acid (CV-11974), and

its prodrug, (+)-1-(cyclohexyloxy)carbonyloxyethyl

2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-1H-benzimidazole-7-carboxylate (TCV-116)

SO Journal of Pharmacology and Experimental Therapeutics (1993),

(FILE 'HOME' ENTERED AT 10:30:26 ON 07 MAR 2006)

FILE 'CAPLUS' ENTERED AT 10:34:21 ON 07 MAR 2006

L1 31 S NEUROTROPH? (L) PYRROLIDIN?
L2 4 S L1 AND PY<1998
L3 0 S PYROLIDIN? (L) (CARBOXYLIC (L) CARBOXYLATE (L) PRODRUG?)
L4 0 S NEUROTROPH? AND (CARBOXYLIC (L) CARBOXYLATE (L) PRODRUG?)
L5 22 S (CARBOXYLIC (L) CARBOXYLATE (L) PRODRUG?)
L6 7 S L5 AND PY<1998
L7 ANALYZE L2 4 RN : 26 TERMS

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L8 26 S L7
L9 0 S L8 AND PYRROLIDIN?

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L10 ANALYZE L2 1-3 RN : 173 TERMS

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* effective March 20, 2005. A new display format, IDERL, is now *
* available and contains the CA role and document type information. *
*

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REGISTRY includes numerically searchable data for experimental and
predicted properties as well as tags indicating availability of
experimental property data in the original document. For information
on property searching in REGISTRY, refer to:

<http://www.cas.org/ONLINE/UG/regprops.html>

=> s l10

L11 173 L10

=> s l11 and pyrrolidin?

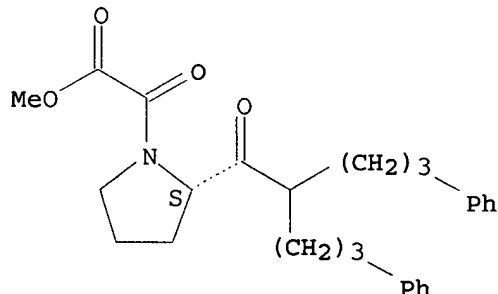
548140 PYRROLIDIN?

L12 18 L11 AND PYRROLIDIN?

=> d scan

L12 18 ANSWERS REGISTRY COPYRIGHT 2006 ACS on STN
IN 1-Pyrrolidineacetic acid, α -oxo-2-[1-oxo-5-phenyl-2-(3-
phenylpropyl)pentyl]-, methyl ester, (2S)- (9CI)
MF C27 H33 N O4

Absolute stereochemistry.

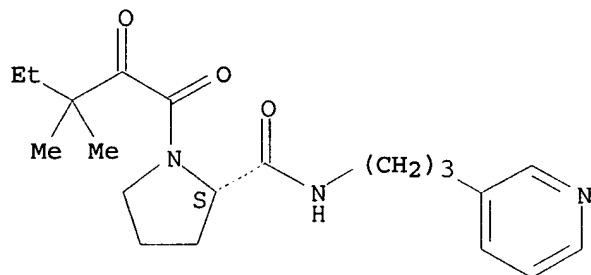


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

HOW MANY MORE ANSWERS DO YOU WISH TO SCAN? (1):17

L12 18 ANSWERS REGISTRY COPYRIGHT 2006 ACS on STN
IN 2-Pyrrolidinecarboxamide, 1-(3,3-dimethyl-1,2-dioxopentyl)-N-[3-(3-pyridinyl)propyl]-, (2S)- (9CI)
MF C20 H29 N3 O3

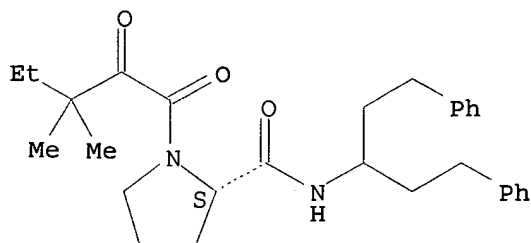
Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L12 18 ANSWERS REGISTRY COPYRIGHT 2006 ACS on STN
IN 2-Pyrrolidinecarboxamide, 1-(3,3-dimethyl-1,2-dioxopentyl)-N-[3-phenyl-1-(2-phenylethyl)propyl]-, (2S)- (9CI)
MF C29 H38 N2 O3

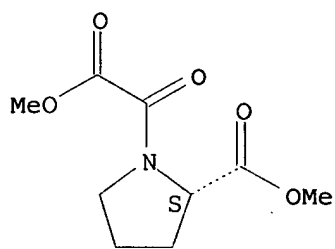
Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L12 18 ANSWERS REGISTRY COPYRIGHT 2006 ACS on STN
IN 1-Pyrrolidineacetic acid, 2-(methoxycarbonyl)- α -oxo-, methyl ester, (2S)- (9CI)
MF C9 H13 N O5

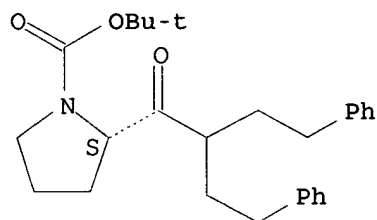
Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L12 18 ANSWERS REGISTRY COPYRIGHT 2006 ACS on STN
 IN 1-Pyrrolidinecarboxylic acid, 2-[1-oxo-4-phenyl-2-(2-phenylethyl)butyl]-, 1,1-dimethylethyl ester, (2S)- (9CI)
 MF C27 H35 N O3

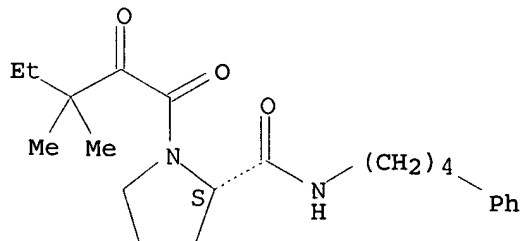
Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L12 18 ANSWERS REGISTRY COPYRIGHT 2006 ACS on STN
 IN 2-Pyrrolidinecarboxamide, 1-(3,3-dimethyl-1,2-dioxopentyl)-N-(4-phenylbutyl)-, (2S)- (9CI)
 MF C22 H32 N2 O3

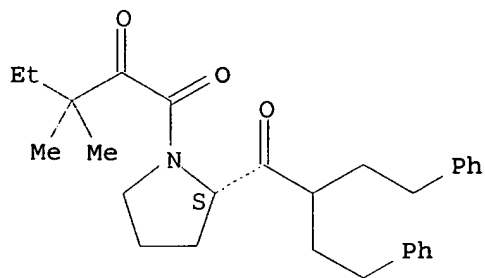
Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L12 18 ANSWERS REGISTRY COPYRIGHT 2006 ACS on STN
 IN Pyrrolidine, 1-(3,3-dimethyl-1,2-dioxopentyl)-2-[1-oxo-4-phenyl-2-(2-phenylethyl)butyl]-, (2S)- (9CI)
 MF C29 H37 N O3

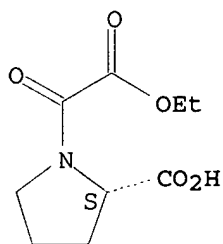
Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L12 18 ANSWERS REGISTRY COPYRIGHT 2006 ACS on STN
IN 1-Pyrrolidineacetic acid, 2-carboxy- α -oxo-, α -ethyl
ester, (2S)- (9CI)
MF C9 H13 N O5
CI COM

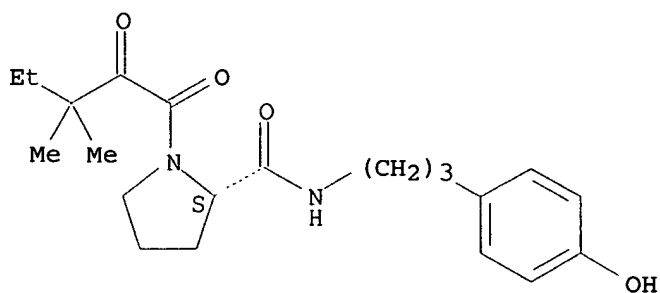
Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L12 18 ANSWERS REGISTRY COPYRIGHT 2006 ACS on STN
IN 2-Pyrrolidinecarboxamide, 1-(3,3-dimethyl-1,2-dioxopentyl)-N-[3-(4-
hydroxyphenyl)propyl]-, (2S)- (9CI)
MF C21 H30 N2 O4

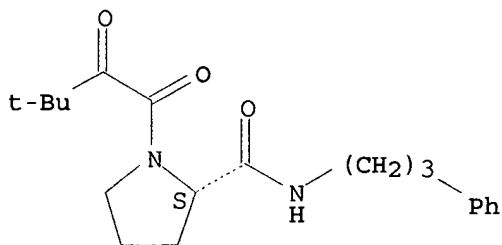
Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L12 18 ANSWERS REGISTRY COPYRIGHT 2006 ACS on STN
 IN 2-Pyrrolidinecarboxamide, 1-(3,3-dimethyl-1,2-dioxobutyl)-N-(3-phenylpropyl)-, (2S)- (9CI)
 MF C20 H28 N2 O3

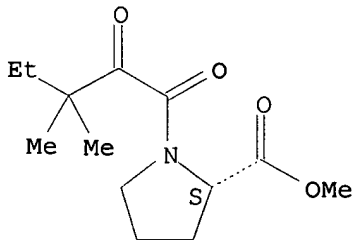
Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L12 18 ANSWERS REGISTRY COPYRIGHT 2006 ACS on STN
 IN L-Proline, 1-(3,3-dimethyl-1,2-dioxopentyl)-, methyl ester (9CI)
 MF C13 H21 N O4

Absolute stereochemistry.

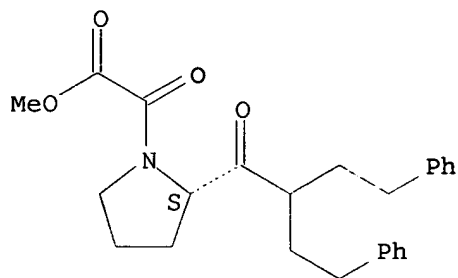


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L12 18 ANSWERS REGISTRY COPYRIGHT 2006 ACS on STN
 IN 1-Pyrrolidineacetic acid, alpha-oxo-2-[1-oxo-4-phenyl-2-(2-phenylethyl)butyl]-, methyl ester, (2S)- (9CI)

MF C25 H29 N O4

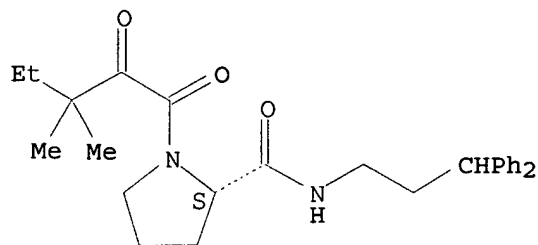
Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L12 18 ANSWERS REGISTRY COPYRIGHT 2006 ACS on STN
IN 2-Pyrrolidinecarboxamide, 1-(3,3-dimethyl-1,2-dioxopentyl)-N-(3,3-diphenylpropyl)-, (2S)- (9CI)
MF C27 H34 N2 O3

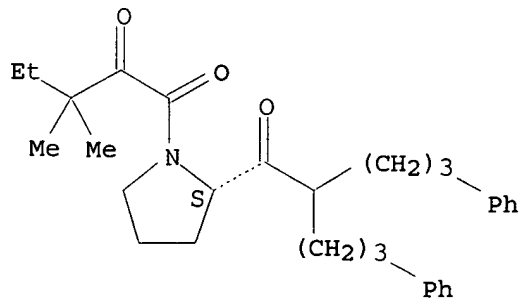
Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L12 18 ANSWERS REGISTRY COPYRIGHT 2006 ACS on STN
IN Pyrrolidine, 1-(3,3-dimethyl-1,2-dioxopentyl)-2-[1-oxo-5-phenyl-2-(3-phenylpropyl)pentyl]-, (2S)- (9CI)
MF C31 H41 N O3

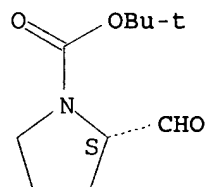
Absolute stereochemistry.



****PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT****

L12 18 ANSWERS REGISTRY COPYRIGHT 2006 ACS on STN
IN 1-Pyrrolidinecarboxylic acid, 2-formyl-, 1,1-dimethylethyl ester,
(2S)- (9CI)
MF C10 H17 N O3

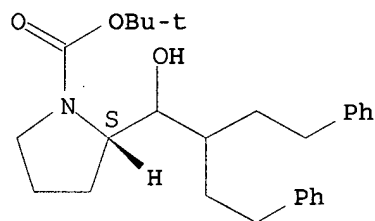
Absolute stereochemistry. Rotation (-).



****PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT****

L12 18 ANSWERS REGISTRY COPYRIGHT 2006 ACS on STN
IN 1-Pyrrolidinecarboxylic acid, 2-[1-hydroxy-4-phenyl-2-(2-phenylethyl)butyl]-, 1,1-dimethylethyl ester, (2S)- (9CI)
MF C27 H37 N O3

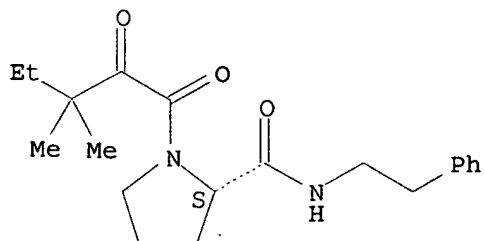
Absolute stereochemistry.



****PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT****

L12 18 ANSWERS REGISTRY COPYRIGHT 2006 ACS on STN
IN 2-Pyrrolidinecarboxamide, 1-(3,3-dimethyl-1,2-dioxopentyl)-N-(2-phenylethyl)-, (2S)- (9CI)
MF C20 H28 N2 O3

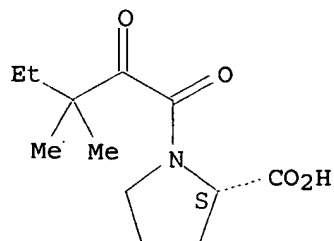
Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L12 18 ANSWERS REGISTRY COPYRIGHT 2006 ACS on STN
IN L-Proline, 1-(3,3-dimethyl-1,2-dioxopentyl)- (9CI)
MF C12 H19 N O4

Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

ALL ANSWERS HAVE BEEN SCANNED